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Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cohort study

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ABSTRACT

Objectives To estimate the prevalence of long-COVID symptoms in children with and without a history of SARS-CoV-2 infection and to evaluate factors associated with long-COVID.

Design A nationwide cohort study

Setting Primary care

Participants 3,240 parents of children aged 5-18 with and without SARS-CoV-2 infection completed an online questionnaire (11.9% response rate); 1,148 and 2,092 with/without a history of infection, respectively.

Primary and secondary outcome measures Primary outcome was the prevalence of long-COVID symptoms in children with/without a history of infection. Secondary outcomes were the factors associated with the presence of long-COVID symptoms and with failure to return to baseline health status in children with a history of infection including gender, age, time from illness, symptomatic illness and vaccine status.

Results

Most long-COVID symptoms were more prevalent in children with a history of SARS-CoV-2 infection; headaches (18.4% vs. 5.4%, PV<0.001), weakness (15.1% vs. 3.3%, PV<0.001), fatigue (12.3% vs. 6.4%, PV<0.001), and abdominal pain (9.5% vs. 3.8%, PV<0.001). Most long-COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12-18) compared to the younger age group (5-11). Some symptoms were more prevalent in children without a history of SARS-CoV-2 infection, including attention problems with school malfunctioning (10.8% vs. 8.5%, PV=0.05), stress (9.1% vs. 5.7%, PV<0.001), social problems (7.8% vs. 2.8%), and weight changes (6.8% vs. 3.7%, PV<0.001)

Conclusion

This study suggests that the prevalence of long-COVID symptoms in children with a history of SARS-CoV-2 infection is high and is more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Strengths and limitations of this study

- A nationwide coverage of participants.
- A relatively large number of participants with a broad age range (5 to 18 years old).
- A comparison of children with or without a history of SARS-CoV-2 infection.
- A relatively low response rate (11.9%) which may cause a selection bias.
- The responses were from a proxy (the parent) rather than the child itself.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in December 2019 and was declared a pandemic by the WHO in March 2020. Evidence emerged slowly but consistently about persistent symptoms following infection and the WHO defined the Post-COVID-19 condition (also known as long-COVID) in October 2021. (1) Reports were first made for adults,(2–4) and later evidence started to emerge regarding the existence of long-COVID in children and adolescents; the first scientific report came from Sweden with a case series by Ludvigsson, who followed five children with a potential long COVID syndrome.(5) First reports were primarily descriptive, with relatively small sample sizes and without a control group.(6)

Behnood et al. performed a meta-analysis of controlled and uncontrolled studies regarding long-COVID in children and adolescents.(7) Among all studies, only five were controlled studies.(8–12) They found a higher prevalence of cognitive difficulties, headache, loss of smell, sore throat, and sore eyes in test-positive children. However, symptoms like abdominal pain, cough, fatigue, myalgia, insomnia, diarrhea, fever, dizziness, or dyspnea were not significantly increased in test-positive children in this study. Controversy later emerged when some of the largest studies about long-COVID in children and adolescents reported different results of prevalence of at least one long-COVID symptom with ranges varying between 1.8% to 61.9%.(8–11,13)

This study aimed to estimate the prevalence of long-COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection and evaluate factors associated with long-COVID and failure to return to baseline health status.

METHODS

Study design and setting

We designed a nationwide cohort study using the centralized database of Maccabi Healthcare Services (MHS), the second-largest healthcare maintenance organization in Israel, which covers 2.6 million citizens and provides a representative sample of the Israeli population. We sent an online questionnaire using text messages to parents of children aged 5-18 years old with a positive Polymerase Chain Reaction (PCR) test for SARS-CoV-2 one to six months before data collection. In addition, we sent the questionnaire to a control group of parents of children with no positive PCR results (with a ratio of 1:2). We asked parents to choose one child per family and answer the questionnaire according to his or her health status (The questionnaire is available as a supplementary file). Informed consent was given via the online questionnaire.

Variables

Demographic and medical variables included age, sex, native-born, height, weight, and the presence of any chronic illness (including diabetes mellitus, asthma, inflammatory disease, oncologic disease, anxiety, or depression). COVID-19-related variables included details about the acute illness, including the date of illness, presence of any symptoms (without mentioning which ones), whether the child was admitted to a hospital due to COVID-19, and if so, whether oxygen supply was warranted, and vaccination status against COVID-19. The last section included questions regarding the presence of Long-COVID symptoms (including physical and mental health symptoms) and asked parents whether the overall health status of their children is worse, the same, or better than their baseline health status. The questionnaire was created by the authors of this study related to most symptoms reported in the literature.

Statistical analysis

Sample size calculations – to show a difference of relatively rare symptoms, we assumed a prevalence of 0.5% in children without and 3.5% in children with a history of SARS-CoV-2 infection. To show a significant difference with a power of 80% and alpha of 5% with a 2:1 ratio, we needed at least 275 in children with, and 550 in children without a history of SARS-CoV-2 infection. We assumed a prevalence of 5% in children without and 10% in children with a history of SARS-CoV-2 infection for more prevalent symptoms. In the same terms, we needed at least 341 in children with and 682 in children without a history of SARS-CoV-2 infection.

Descriptive statistics were used for all variables, with absolute numbers and percentages for categorical variables and mean and standard deviation for continuous variables. First, we performed univariate analysis to all long-COVID symptoms and compared children with and without a history of SARS-CoV-2 infection using the chi-square test. We then performed the same analysis with age stratification (ages 5-11 and 12-18). Next, we performed two sets of multi-variable tests to examine which factors were associated with having at least one long-COVID symptom and which factors were associated with worse health status than baseline health status. Both analyses were made using a logistic regression analysis with two blocks, the first using the ENTER approach for baseline characteristics and the FORWARD approach for more elaborated variables. Last, we performed a univariate analysis of the differences between parents of children who did and did not answer the questionnaire. We used the Statistical Package for Social Sciences (SPSS) software version 28 for data analysis.

Ethics statement

The MHS Institutional Review Board (IRB) approved this study (ID 0169-20-MHS).

Patient and public involvement

No patients involved.

RESULTS

Study population

In December 2021 and January 2022, we sent the online questionnaire to 27,240 parents of children (8,550 of parents had at least one child with a history of SARS-CoV-2 infection). 3,240 parents answered the questionnaire and agreed to participate in the study (11.9% response rate). Of all respondents, 1,148 children had a history of SARS-CoV-2 infection, and 2,092 children had no history of SARS-CoV-2 infection. The average age of children with and without a history of SARS-CoV-2 infection was 10.8 and 9.5, with 63.7% and 61.3% females, respectively (Table 1).

Table 1. Characteristics of children with and without a history of SARS-CoV-2 infection

	Children with a history of SARS-CoV-2 infection	**Children without a history of SARS-CoV-2 infection**
	N=1,148	N=2,092
Age, mean ± standard deviation	10.8 ± 0.08	9.5 ± 0.09
Background variables	n (%)	n (%)
Females	731 (63.7)	1,282 (61.3)
Native born	931 (81)	1,635 (78.1)
Any regular medications	88 (7.7)	188 (10.6)
Diabetes mellitus	4 (0.35)	4 (0.2)
asthma	20 (1.7)	21 (1)

Inflammatory / immune disease	6 (0.5)	17 (0.8)
Depression / anxiety	9 (0.8)	18 (0.9)
A history of any oncologic disease	2 (0.2)	4 (0.2)
COVID-related variables	n (%)	n (%)
At least 1 vaccination	172 (15)	1424 (68)
Symptomatic COVID-19	720 (62.7)	
Hospitalization due to COVID-19	4 (0.3)	
Time since COVID-19 infection (months) Mean ± SD Range	 4.39 ± 1.5 Range: 1-12 months	

Parents of children with and without a history of SARS-CoV-2 infection shared similar characteristics (Table 2).

Table 2. Characteristics of parents who did or did not respond to the questionnaire

	Respondents (N=3,778)	Entire cohort (N=27,247)
	n (%)	n (%)
Females	2,310 (61.1)	14,880 (54.6)
Age <24 25-34 35-44 45-54 >55	 1 (0.03) 221 (5.8) 1,441 (38.1) 1,749 (46.3) 366 (9.7)	 10 (0.04) 2,182 (8) 10,657 (39.1) 11,829 (43.4) 2,569 (9.4)
Sector		

Orthodox-Jewish	115 (3)	956 (3.5)
Arab	109 (2.9)	2021 (7.4)
All other	3,554 (94.1)	24,270 (89.1)

Of all children with a history of SARS-CoV-2 infection, 720 (62.7%) had symptomatic COVID-19, four were hospitalized due to COVID-19 (0.3%), and 1 needed oxygen supply. The mean duration between infection and answering the questionnaire was 4.4 months. Overall, 696 (33.3%) children without and 502 (43.7%) children with a history of SARS-CoV-2 infection reported at least one symptom (PV<0.001) and 89 (4.3%) children without and 114 (9.9%) children with a history of SARS-CoV-2 infection reported at least five symptoms (PV<0.001). In addition, 113 (5.4%) children without and 107 (9.3%) children with a history of SARS-CoV-2 infection reported an inability to return to their baseline health status (PV<0.001) (Table 3).

Table 3. Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection

	No history of SARS-CoV2-infection	**With a history of SARS-Cov-2 infection**	**P-value**
	N= 2,092 n (%)	**N= 1,148 n (%)**	
No reported symptoms	1396 (66.7)	646 (56.3)	
≥ 1 symptom	696 (33.3)	502 (43.7)	<0.001
≥ 5 symptoms	89 (4.3)	114 (9.9)	<0.001
Current health status compared to before illness/pandemia - worse	113 (5.4)	107 (9.3)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection			
Headaches	114 (5.4)	211 (18.4)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001

Fatigue	133 (6.4)	141 (12.3)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001
Cough	49 (2.3)	101 (8.8)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001
Memory disturbances	18 (0.9)	51 (4.4)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001
Dyspnea	20 (1)	31 (2.7)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection			
Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001
Social problems	164 (7.8)	32 (2.8)	<0.001
Weight changes	143 (6.8)	43 (3.7)	<0.001
Sleep disturbance	103 (4.9)	34 (3.0)	0.008
Hearing disturbances	7 (0.3)	0 (0)	0.056
Symptoms with non-significant results			
Decreased mood	163 (7.8)	69 (6)	0.064
Rash	18 (0.9)	13 (1.1)	0.455
Visual disturbance	22 (1.1)	14 (1.2)	0.727
Hearing disturbances	7 (0.3)	0 (0)	0.056

Long-COVID symptoms

The five most prevalent long-COVID symptoms reported by parents of children with compared to children without a history of SARS-CoV-2 infection were headaches (18.4% vs. 5.4%, PV<0.001), weakness (15.1% vs. 3.3%, PV<0.001), fatigue (12.3%

vs. 6.4%, PV<0.001), abdominal pain (9.5% vs. 3.8%, PV<0.001) and cough (8.8% vs. 2.3%, PV<0.001) (Figure 1). Other more prevalent symptoms in children with a history of SARS-CoV-2 infection were myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnea, and increased heart rate (Table 3).

Most long-COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12-18) compared to the younger age group (5-11), including headaches (25% vs. 19%, PV-0.05), weakness (26.8% vs. 13.7%, PV<0.001), fatigue (28.6% vs. 9.4%, PV<0.001), taste (14.3% vs. 3.4%, PV<0.001), smell (16.1% vs. 3.8%, PV<0.001), myalgia (15.2% vs. 8%, PV-0.002), decreased mood (12.9% vs. 4.9%, PV<0.001) and attention (13.4% vs. 8.3%, PV-0.028). None of the symptoms were more prevalent in the younger age group (Table 1S, Figure 2).

Symptoms more prevalent in children without a history of SARS-CoV-2 infection were attention problems with school malfunctioning (10.8% vs. 8.5%, PV=0.05), stress or increased worries (9.1% vs. 5.7%, PV<0.001), social problems (7.8% vs. 2.8%), weight changes (6.8% vs. 3.7%, PV<0.001) and sleep disturbances (4.9%, vs. 3%, PV=0.008). All these symptoms were more prevalent in the older age group. However, in the older age group, all these symptoms were not significantly different between children with or without a history of SARS-CoV-2 infection (Table 1S).

Symptoms which were not found significantly different between children with or without a history of SARS-CoV-2 infection include decreased mood (6% vs. 7.8%, PV=0.064), rash (1.1% vs. 0.9%, PV=0.455, visual disturbances (1.2% vs. 1.1%, PV=0.727) and hearing problems (0% vs. 0.3%, PV=0.056).

Multivariate analysis

Factors associated with at least one long-COVID symptom include older age and a history of symptomatic COVID infection. Each one-year increment in age increases the risk in 8% (odds ratio [OR] 1.08, 95% confidence interval (CI) 1.03-1.14, PV=0.001). The history of symptomatic COVID infection increases the risk substantially, OR-4.41, 95% CI 3.27-5.94, PV<0.001) (Table 2S).

Failure (or inability) to return to baseline health status in children with a history of SARS-CoV-2 infection was associated with fatigue (OR-9.71, 95% CI 5.58-16.87, PV<0.001), weight changes (OR- 4.75, 95% CI 1.92-11.76, PV<0.001), decreased social functioning (OR-4.58, 95% CI 1.64-12.77, PV=0.004), dyspnea (OR-3.35, 95% CI 1.16-9.63, PV=0.025), increased stress (OR-2.97, 95% CI 1.37-6.43, PV=0.006), dizziness (OR-2.75, 95% CI 1.17-6.49, PV=0.021), headaches (OR-2.70, 95% CI 1.52-4.80, PV<0.001) and attention disturbances with malfunction in school (OR-2.19, 95% CI 1.12-4.26, PV=0.022) (Table 3S). Age, gender, time from illness, symptomatic disease, and vaccination status were not associated with not returning to baseline health status in test-positive children.

DISCUSSION

Principal findings

We conducted a nationwide cohort study to assess the prevalence of long-COVID symptoms reported by the parents of children with or without a history of SARS-CoV-2 infection. In addition, we evaluated the factors associated with the presence of any long-COVID symptom and not returning to baseline state of health.

Children with a history of SARS-CoV-2 infection had significantly more physical symptoms, including headaches, weakness, fatigue, abdominal pain, cough, myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness,

arthralgia, chest pain, dyspnea, and increased heart rate. Children without a history of SARS-CoV-2 infection had significantly more functional symptoms, including attention problems with a malfunction in school, stress or increased worries, social problems, weight changes, and sleep disturbances. Almost all symptoms were more prevalent among the older age group than the younger age group.

Factors associated with at least one long-COVID symptom were age and symptomatic SARS-CoV-2 infection. Factors associated with not returning to baseline health status were long-COVID symptoms, including fatigue, weight changes, decreased social functioning, dyspnea, increased stress, dizziness, headache, and attention disturbances with malfunction at school.

Strengths and limitations

The strengths of this study are its nationwide coverage, the relatively large number of participants, the comparison of children with or without a history of SARS-CoV-2 infection, and the broad age range (5 to 18 years old).

The limitations of this study are its relatively low response rate (11.9%) which may cause a selection bias, the responses from a proxy (a parent) rather than the child itself, and the potential for differential misclassification bias as parents to children with a history of SARS-CoV-2 infection may report more symptoms than children without a history of SARS-CoV-2 infection. We have compared the parents who did and did not respond to our survey to reduce this possible selection bias. Another limitation is the option we have given parents regarding which child they choose to report the symptoms in the questionnaire.

Interpretation

We report a high rate of at least one long-COVID symptom in both children with or without a history of SARS-CoV-2 infection (43.7% vs. 33.3). This is in line with

other studies that found similar rates of long-COVID symptoms, including 35.4% vs. 8.3% in the CLOCK study and 61.9% vs. 57% in the LongCOVIDKidsDK.(9,13) However, other studies reported much lower rates of having at least one long-COVID symptom, including Molteni et al. with only 4.4% after 28 days and 1.8% at 56 days, Radtke et al. with 4% vs. 2%, and Zavala et al. with 6.7% vs. 4.2%.(8,10,12) These differences were addressed by Molteni herself and explained by some possible reasons; different study design, different response rates (and thus a better or worse representation of the entire pediatric population), gender imbalance, recall bias, and the higher awareness for this syndrome due to extensive media coverage.(14)

The presence of at least five symptoms in our study is 9.9% vs. 4.3%, lower than the rate reported by the CLOCK study (23.7% vs. 3.8%). The age differences in both studies can explain this. The CLOCK focused mainly on adolescents, whereas our study age range was 5-18, with a median age of 10.8 and 9.5 in test-positive and test-negative children, respectively.

The five most prevalent long-COVID symptoms reported by parents of children with vs. without a history of SARS-CoV-2 infection were headaches, weakness, fatigue, abdominal pain, and cough. In Behnood et al.'s meta-analysis, headache, loss of smell, sore throat, and sore eyes were more prevalent in test-positive than test-negative children(7). However, abdominal pain, cough, fatigue, myalgia, insomnia, diarrhea, fever, dizziness, and dyspnea were similarly prevalent in both groups. It is important to note that the LongCOVIDKidsDK was not included in this meta-analysis. In this study, the most prevalent symptoms were dyspnea, cough, sore throat, dizziness, and chest pain.(13) The symptoms in children are similar to the symptoms most commonly reported by adults. This includes weakness, general malaise, fatigue, dyspnea, arthralgia, and headache (15–18).

Interestingly, our study found that some symptoms were more prevalent in children without a history of previous SARS-CoV-2 infection, including attention with malfunction in school, stress or increased worries, social problems, weight changes, and sleep disturbances. These are all functional complaints that may reflect life's impact during the pandemic on children. Notably, no significant difference in these symptoms existed in the older age group in adolescents with or without a history of SARS-CoV-2 infection. This is in line with the results of Blankenburg et al., which reported a lack of differences in neurocognitive, general pain, and most mood symptoms with a very high rate of reported symptoms (at least 35%) regardless of serostatus (11). This highlights the impact of the pandemic itself, rather than being infected, as a significant source of stress, decreased mood, and poor quality of life for children and adolescents.(19–22)

We found that the presence of any long-COVID symptom was associated with older age and a history of a symptomatic disease but not with gender. Older age and female gender were associated with long-COVID symptoms in children and adolescents in most studies.(7,9–11) In adults, risk factors for long-COVID symptoms include age, female gender, and the history of symptomatic disease. (23–25)

Conclusion

This study suggests that the prevalence of long-COVID symptoms in children with a history of SARS-CoV-2 infection is high and is more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Contribution Statement

Dr. Adler conceptualized and designed the study, designed the data collection instruments, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Israel designed the data collection instruments, collected data, and reviewed and revised the manuscript.

Dr. Yehoshua, Prof. Azuri, Dr. Hoffman, Dr. Shahar, and Dr. Mizrahi Reuveni conceptualized and designed the study and reviewed and revised the manuscript.

Prof. Grossman conceptualized and designed the study, designed the data collection instruments, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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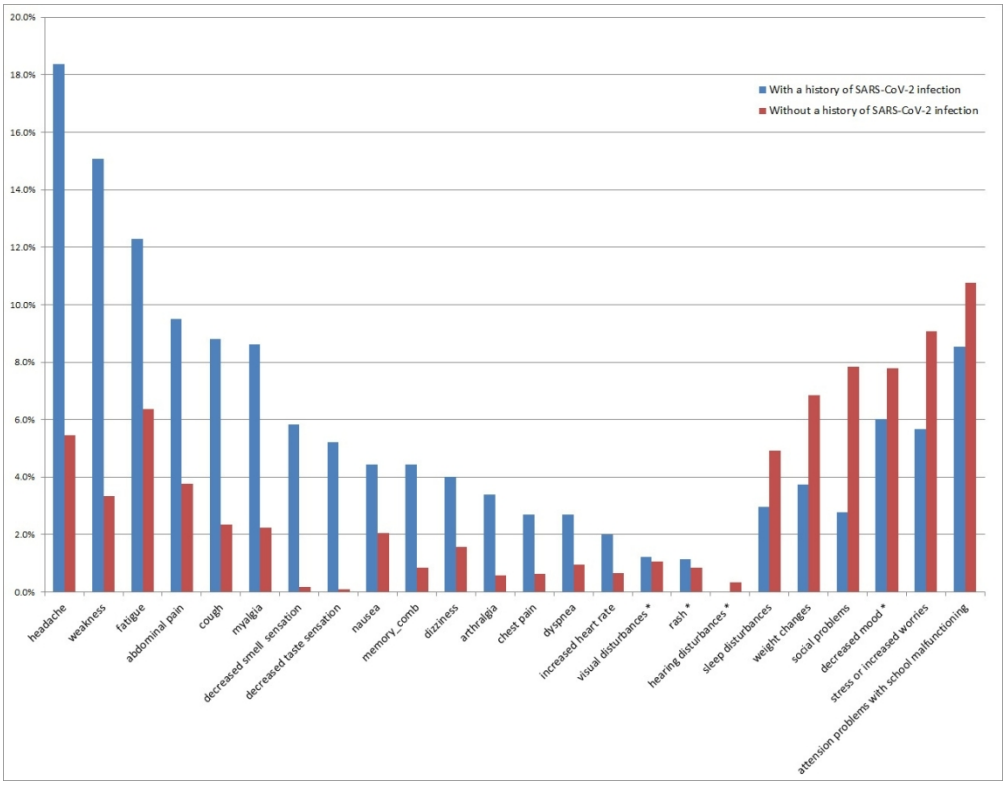
Figure 1. Rates of long-COVID symptoms in children with and without a history of SARS-CoV-2 infection

Long-COVID symptoms with insignificant differences are marked with an asterisk (*).

Figure 2. Rates of long-COVID symptoms in children with a history of SARS-CoV-2 infection – a comparison between children aged 5-11 and adolescents aged 12-18

Long-COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).



Long-COVID symptoms with insignificant differences are marked with an asterisk (*).

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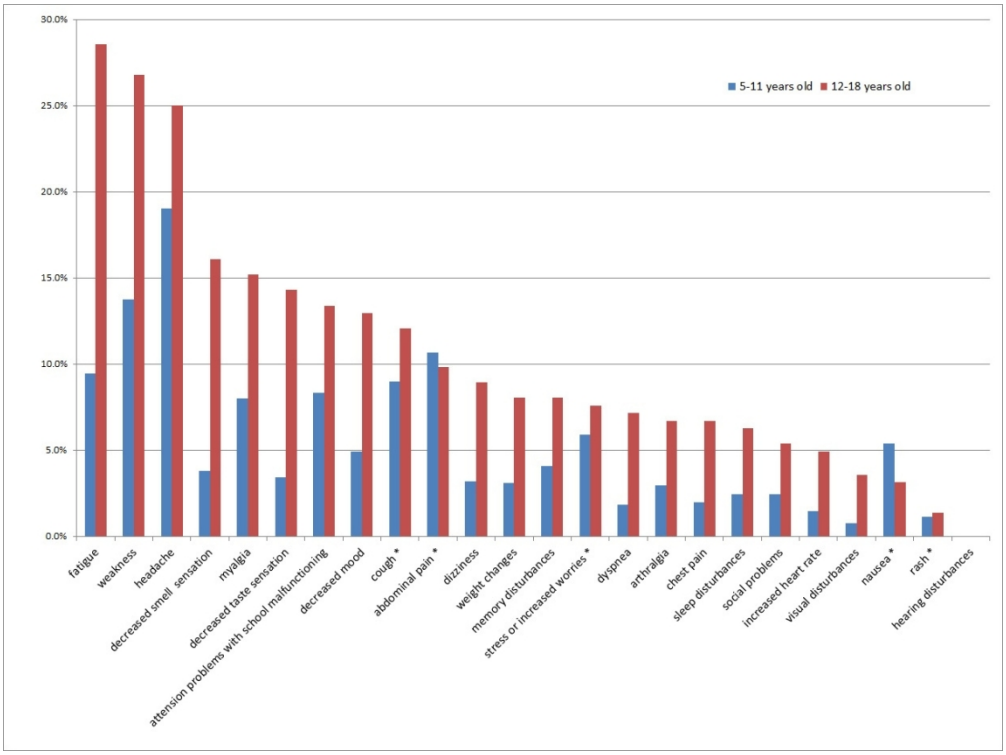

Long-COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).

439x327mm (72 x 72 DPI)

Table 1S. Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection, stratified by age and infection status

	All participants			Participants aged 5-11*			Participants aged 12-18*		
	No history of SARS-CoV2-infection	**With a history of SARS-Cov-2 infection**	**P-value**	**No history of SARS-CoV2-infection**	**With a history of SARS-Cov-2 infection**	**P-value**	**No history of SARS-CoV2-infection**	**With a history of SARS-Cov-2 infection**	**P-value**
	N= 2,092 n (%)	**N= 1,148 n (%)**		**n=1218**	**n=815**		**N=817**	**N=224**	
No reported symptoms	1396 (66.7)	646 (56.3)	<0.001	831 (68.2)	450 (55.2)	<0.001	508 (62.2)	88 (39.3)	<0.001
≥ 1 symptom	696 (33.3)	502 (43.7)		387 (31.8)	365		309 (37.8)	136 (60.7)	

					(44.8)				
≥ 5 symptoms	89 (4.3)	114 (9.9)	<0.001	35 (2.9)	66 (8.1)	<0.001	54 (6.6)	48 (21.4)	<0.001
Current health status compared to before illness/pandemia worse	113 (5.4)	107 (9.3)	<0.001	47 (3.9)	64 (7.9)	<0.001	66 (8.1)	43 (19.2)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection									
Headaches	114 (5.4)	211 (18.4)	<0.001	56 (4.6)	155 (19)	<0.001	58 (7.1)	56 (25%)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001	27 (2.2)	112 (13.7)	<0.001	43 (5.3)	60 (26.8)	<0.001
Fatigue	133 (6.4)	141 (12.3)	<0.001	33 (2.7)	77 (9.4)	<0.001	100 (12.2)	64 (28.6)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001	49 (4)	87 (10.7)	<0.001	30 (3.7)	22 (9.8)	<0.001

Cough	49 (2.3)	101 (8.8)	<0.001	32 (2.6)	73 (9)	<0.001	17 (2.1)	27 (12.1)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001	24 (2)	65 (8)	<0.001	23 (2.8)	34 (15.2)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001	1 (0.1)	31 (3.8)	<0.001	3 (0.4)	36 (16.1)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001	1 (0.1)	28 (3.4)	<0.001	1 (0.1)	32 (14.3)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001	21 (1.7)	44 (5.4)	<0.001	22 (2.7)	7 (3.1)	0.818
Memory disturbances	18 (0.9)	51 (4.4)	<0.001	13 (1.1)	33 (4)	<0.001	5 (0.6)	18 (8)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001	11 (0.9)	26 (3.2)	<0.001	22 (2.7)	20 (8.9)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001	6 (0.5)	24 (2.9)	<0.001	6 (0.7)	15 (6.7)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001	5 (0.4)	16 (2)	<0.001	8 (1)	15 (6.7)	<0.001
Dyspnea	20 (1)	31 (2.7)	<0.001	8 (0.7)	15 (1.8)	0.013	12 (1.5)	16 (7.1)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001	6 (0.5)	12 (1.5)	0.021	8 (1)	11 (4.9)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection									

Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05	133 (10.9)	68 (8.3)	0.057	92 (11.3)	30 (13.4)	0.412
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001	112 (9.2)	48 (5.9)	0.007	78 (9.5)	17 (7.6)	0.433
Social problems	164 (7.8)	32 (2.8)	<0.001	87 (7.1)	20 (2.5)	<0.001	77 (9.4)	12 (5.4)	0.059
Weight changes	143 (6.8)	43 (3.7)	<0.001	71 (5.8)	25 (3.1)	0.004	72 (8.8)	18 (8)	0.789
Sleep disturbance	103 (4.9)	34 (3.0)	0.008	47 (3.9)	20 (2.5)	0.082	56 (6.9)	14 (6.3)	0.768
Symptoms with non-significant results									
Decreased mood	163 (7.8)	69 (6)	0.064	69 (5.7)	40 (4.9)	0.458	94 (11.5)	29 (12.9)	0.560
Rash	18 (0.9)	13 (1.1)	0.455	11 (0.9)	9 (1.1)	0.652	7 (0.9)	3 (1.3)	0.699
Visual disturbance	22 (1.1)	14 (1.2)	0.727	12 (1)	6 (0.7)	0.557	10 (1.2)	8 (3.6)	0.024
Hearing disturbances	7 (0.3)	0 (0)	0.056	4 (0.3)	0 (0)	0.102	3 (0.4)	0 (0)	0.602

*children whose parents did not declare age were excluded from the age stratification

Table 2S. Multivariate analysis of children with a history of SARS-CoV-2 infection who reported at least one symptom of long COVID-19

Variable	Odds Ratio (95% Confidence interval)	P value
Age †	1.08 (1.03, 1.14)	0.001
Sex (female) †	1.12 (0.84, 1.48)	0.442
Time from illness †	0.95 (0.86, 1.05)	0.311
Symptomatic COVID-19 †	4.41 (3.27, 5.94)	<0.001
Vaccination against COVID-19 †	0.87 (0.58, 1.31)	0.512

† Symptomatic disease, age, sex, time from illness, and vaccination status were entered with ENTER method
(*) The presence of diabetes mellitus, asthma, auto-immune disease, a history of malignancy, and native-born were entered with the FORWARD method. None were found significant and entered the final model.

Table 3S. Multivariate analysis of children with a history of SARS-CoV-2 infection who reported their overall health state is worse than before the illness

Variable	Odds Ratio (95% Confidence interval)	P value
Age †	1.06 (0.96, 1.16)	0.257
Sex (female) †	1.06 (0.60, 1.88)	0.833
Time from illness †	0.94 (0.77, 1.16)	0.579
Symptomatic disease †	1.93 (0.93, 4.04)	0.079
Vaccination	1.25 (0.59, 2.65)	0.556
fatigue	9.71 (5.58, 16.87)	<0.001
Weight changes	4.75 (1.92, 11.76)	<0.001
Decreased social function	4.58 (1.64, 12.77)	0.004
Dyspnea ‡	3.35 (1.16, 9.63)	0.025
Increased stress	2.97 (1.37, 6.43)	0.006
Dizziness	2.75 (1.17, 6.49)	0.021
Headache ‡	2.70 (1.52, 4.80)	<0.001
Attention disturbances with impact on functioning in school	2.19 (1.12, 4.26)	0.022

†age, sex, time from illness, symptomatic disease, and vaccination status were entered with ENTER method
‡ Long COVID-19 symptoms (fatigue, decreased smell sensation, decreased taste sensation, headache, dyspnea, myalgia, cough, rash, nausea, weakness, depression, stress, memory disturbances, confusion, dizziness, sleep disturbances, arthralgia, abdominal pain, chest pain, increased heart rate, disturbed vision, hearing disturbances, weight changes, attention disturbances with impact on school and decreased social functioning) were entered with FORWARD method

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cross-sectional study

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Keywords:	COVID-19, EPIDEMIOLOGY, PAEDIATRICS, PRIMARY CARE

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Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cross-sectional study

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Word count: 2,728

ABSTRACT

Objectives To estimate the prevalence of long-COVID symptoms in children with and without a history of SARS-CoV-2 infection and to evaluate factors associated with long-COVID.

Design A nationwide cross-sectional study

Setting Primary care

Participants 3,240 parents of children aged 5-18 with and without SARS-CoV-2 infection completed an online questionnaire (11.9% response rate); 1,148 and 2,092 with/without a history of infection, respectively.

Primary and secondary outcome measures Primary outcome was the prevalence of long-COVID symptoms in children with/without a history of infection. Secondary outcomes were the factors associated with the presence of long-COVID symptoms and with failure to return to baseline health status in children with a history of infection including gender, age, time from illness, symptomatic illness and vaccine status.

Results

Most long-COVID symptoms were more prevalent in children with a history of SARS-CoV-2 infection; headaches (211 [18.4%] vs. 114 [5.4%], p-value [PV]<0.001), weakness (173 [15.1%] vs. 70 [3.3%], PV<0.001), fatigue (141 [12.3%] vs. 133 [6.4%], PV<0.001), and abdominal pain (109 [9.5%] vs. 79 [3.8%], PV<0.001). Most long-COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12-18) compared to the younger age group (5-11). Some symptoms were more prevalent in children without a history of SARS-CoV-2 infection, including attention problems with school malfunctioning (225 [10.8%] vs. 98 [8.5%], PV=0.05), stress (190 [9.1%] vs. 65 [5.7%], PV<0.001),

social problems (164 [7.8%] vs. 32 [2.8%]), and weight changes (143 [6.8%] vs. 43 [3.7%], PV<0.001)

Conclusion

This study suggests that the prevalence of long-COVID symptoms in children with a history of SARS-CoV-2 infection might be higher and more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Strengths and limitations of this study

- A nationwide coverage of participants.
- A relatively large number of participants with a broad age range (5 to 18 years old).
- A comparison of children with or without a history of SARS-CoV-2 infection.
- A relatively low response rate (11.9%) which may cause a selection bias.
- The responses were from a proxy (the parent) rather than the child itself.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in December 2019 and was declared a pandemic by the WHO in March 2020. Evidence emerged slowly but consistently about persistent symptoms following infection and the WHO defined the Post-COVID-19 condition (also known as long-COVID) in October 2021. (1) Reports were first made for adults,(2–4) and later evidence started to emerge regarding the existence of long-COVID in children and adolescents; the first scientific report came from Sweden with a case series by Ludvigsson, who followed five children with a potential long COVID syndrome.(5) First reports were primarily descriptive, with relatively small sample sizes and without a control group.(6)

Behnood et al. performed a meta-analysis of controlled and uncontrolled studies regarding long-COVID in children and adolescents.(7) Among all studies, only five were controlled studies.(8–12) They found a higher prevalence of cognitive difficulties, headache, loss of smell, sore throat, and sore eyes in test-positive children. However, symptoms like abdominal pain, cough, fatigue, myalgia, insomnia, diarrhea, fever, dizziness, or dyspnea were not significantly increased in test-positive children in this study. Controversy later emerged when some of the largest studies about long-COVID in children and adolescents reported different results of prevalence of at least one long-COVID symptom with ranges varying between 1.8% to 61.9% (8–11,13-14).

This study aimed to estimate the prevalence of long-COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection and evaluate factors associated with long-COVID and failure to return to baseline health status.

METHODS

Study design and setting

We designed a nationwide cross-sectional study using the centralized database of Maccabi Healthcare Services (MHS), the second-largest healthcare maintenance organization in Israel, which covers a quarter of Israel's population (2.6 million citizens). We sent an online questionnaire using text messages to parents of children aged 5-18 years old with a positive Polymerase Chain Reaction (PCR) test for SARS-CoV-2 one to six months before data collection. In addition, we sent the questionnaire to a control group of parents of children with no positive PCR results (with a ratio of 1:2). We asked parents to choose one child per family and answer the questionnaire according to his or her health status (The questionnaire is available, supplementary material – part A). The questionnaire did not include questions about other infections. Informed consent was given via the online questionnaire.

Variables

Demographic and medical variables included age, sex, native-born, height, weight, and the presence of any chronic illness (including diabetes mellitus, asthma, inflammatory disease, oncologic disease, anxiety, or depression). COVID-19-related variables included details about the acute illness, including the date of illness, presence of any symptoms (without mentioning which ones), whether the child was admitted to a hospital due to COVID-19, and if so, whether oxygen supply was warranted, and vaccination status against COVID-19. The last section included questions regarding the presence of Long-COVID symptoms (including physical and mental health symptoms, long-COVID symptoms were defined as symptoms lasting more than 4-weeks) and asked parents whether the overall health status of their children is worse, the same, or better than their baseline health status. We chose to

refer to these symptoms as long-COVID symptoms in both groups for reasons of clarity, although long-COVID does not exist in the control group. The questionnaire was created by the authors of this study related to most symptoms reported in the literature.

Statistical analysis

Sample size calculations – to show a difference of relatively rare symptoms, we assumed a prevalence of 0.5% in children without and 3.5% in children with a history of SARS-CoV-2 infection. To show a significant difference with a power of 80% and alpha of 5% with a 2:1 ratio, we needed at least 275 in children with, and 550 in children without a history of SARS-CoV-2 infection. We assumed a prevalence of 5% in children without and 10% in children with a history of SARS-CoV-2 infection for more prevalent symptoms. In the same terms, we needed at least 341 in children with and 682 in children without a history of SARS-CoV-2 infection.

Descriptive statistics were used for all variables, with absolute numbers and percentages for categorical variables and mean and standard deviation for continuous variables. First, we performed univariate analysis to all long-COVID symptoms and compared children with and without a history of SARS-CoV-2 infection using the chi-square test. We then performed the same analysis with age stratification (ages 5-11 and 12-18). Next, we performed two sets of multi-variable tests to examine which factors were associated with having at least one long-COVID symptom and which factors were associated with worse health status than baseline health status. Both analyses were made using a logistic regression analysis with two blocks, the first using all variables (the ENTER approach) for baseline characteristics and forward stepwise selection for more elaborated variables. Last, we performed a univariate analysis of the differences between parents of children who did and did not answer the

questionnaire. We used the Statistical Package for Social Sciences (SPSS) software version 28 for data analysis.

Ethics statement

The MHS Institutional Review Board (IRB) approved this study (ID 0169-20-MHS).

Patient and public involvement

No patients involved.

RESULTS

Study population

In December 2021 and January 2022, we sent the online questionnaire to 27,240 parents of children (8,550 of parents had at least one child with a history of SARS-CoV-2 infection). 3,240 parents answered the questionnaire and agreed to participate in the study (11.9% overall response rate, 13.4% in children with and 11.2% in children without a history of infection). Of all respondents, 1,148 children had a history of SARS-CoV-2 infection, and 2,092 children had no history of SARS-CoV-2 infection. The average age of children with and without a history of SARS-CoV-2 infection was 10.8 and 9.5, with 731 (63.7%) and 1,282 (61.3%) females, respectively (Table 1).

Table 1. Characteristics of children with and without a history of SARS-CoV-2 infection

	Children with a history of SARS-CoV-2 infection	**Children without a history of SARS-CoV-2 infection**
	N=1,148	N=2,092

Age, mean ± standard deviation	10.8 ± 0.08	9.5 ± 0.09
Background variables	n (%)	n (%)
Females	731 (63.7)	1,282 (61.3)
Native born	931 (81)	1,635 (78.1)
Any regular medications	88 (7.7)	188 (10.6)
Diabetes mellitus	4 (0.35)	4 (0.2)
asthma	20 (1.7)	21 (1)
Inflammatory / immune disease	6 (0.5)	17 (0.8)
Depression / anxiety	9 (0.8)	18 (0.9)
A history of any oncologic disease	2 (0.2)	4 (0.2)
COVID-related variables	n (%)	n (%)
At least 1 vaccination	172 (15)	1424 (68)
Symptomatic COVID-19	720 (62.7)	
Hospitalization due to COVID-19	4 (0.3)	
Time since COVID-19 infection (months) Mean ± SD Range	 4.39 ± 1.5 Range: 1-12 months	

Parents of children who did or did not fill the questionnaire shared similar characteristics (Table 2).

Table 2. Characteristics of parents who did or did not respond to the questionnaire

	Respondents (N=3,778)	Non-respondents (N=23,469)	P value
	n (%)	n (%)	
Females	2,310 (61.1)	12,570 (53.6)	<0.001

Age			
<24	1 (0.03)	9 (0.04)	
25-34	221 (5.8)	1,961 (8.3)	
35-44	1,441 (38.1)	9,216 (39.3)	<0.001
45-54	1,749 (46.3)	10,080 (42.9)	
>55	366 (9.7)	2,203 (9.4)	
Sector			
Orthodox-Jewish	115 (3)	841 (3.6)	
Arab	109 (2.9)	1,912 (8.1)	<0.001
All other	3,554 (94.1)	20,716 (88.3)	

Of all children with a history of SARS-CoV-2 infection, 720 (62.7%) had symptomatic COVID-19, four were hospitalized due to COVID-19 (0.3%), and 1 needed oxygen supply. The mean duration between infection and answering the questionnaire was 4.4 months. Overall, 696 (33.3%) children without and 502 (43.7%) children with a history of SARS-CoV-2 infection reported at least one symptom (PV<0.001) and 89 (4.3%) children without and 114 (9.9%) children with a history of SARS-CoV-2 infection reported at least five symptoms (PV<0.001). In addition, 113 (5.4%) children without and 107 (9.3%) children with a history of SARS-CoV-2 infection reported an inability to return to their baseline health status (PV<0.001) (Table 3).

Table 3. Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection

	No history of SARS-CoV2-infection	**With a history of SARS-Cov-2 infection**	**P-value**
	N= 2,092 n (%)	**N= 1,148 n (%)**	

No reported symptoms	1396 (66.7)	646 (56.3)	
≥ 1 symptom	696 (33.3)	502 (43.7)	<0.001
≥ 5 symptoms	89 (4.3)	114 (9.9)	<0.001
Current health status compared to before illness/pandemia - worse	113 (5.4)	107 (9.3)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection			
Headaches	114 (5.4)	211 (18.4)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001
Fatigue	133 (6.4)	141 (12.3)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001
Cough	49 (2.3)	101 (8.8)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001
Memory disturbances	18 (0.9)	51 (4.4)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001
Dyspnea	20 (1)	31 (2.7)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection			
Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001
Social problems	164 (7.8)	32 (2.8)	<0.001
Weight changes	143 (6.8)	43 (3.7)	<0.001
Sleep disturbance	103 (4.9)	34 (3.0)	0.008
Symptoms with non-significant results			
Decreased mood	163 (7.8)	69 (6)	0.064
Rash	18 (0.9)	13 (1.1)	0.455
Visual disturbance	22 (1.1)	14 (1.2)	0.727

Hearing disturbances	7 (0.3)	0 (0)	0.056

Long-COVID symptoms

The five most prevalent long-COVID symptoms reported by parents of children with compared to children without a history of SARS-CoV-2 infection were headaches (211 [18.4%] vs. 114 [5.4%], PV<0.001), weakness (173 [15.1%] vs. 70 [3.3%], PV<0.001), fatigue (141 [12.3%] vs. 133 [6.4%], PV<0.001), abdominal pain (109 [9.5%] vs. 79 [3.8%], PV<0.001) and cough (101 [8.8%] vs. 49 [2.3%], PV<0.001) (Figure 1). Other more prevalent symptoms in children with a history of SARS-CoV-2 infection were myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnea, and increased heart rate (Table 3).

Most long-COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12-18) compared to the younger age group (5-11), including headaches (56 [25%] vs. 155 [19%], PV-0.05), weakness (60 [26.8%] vs. 112 [13.7%], PV<0.001), fatigue (64 [28.6%] vs. 77 [9.4%], PV<0.001), taste (32 [14.3%] vs. 28 [3.4%], PV<0.001), smell (36 [16.1%] vs. 31 [3.8%], PV<0.001), myalgia (34 [15.2%] vs. 65 [8%], PV-0.002), decreased mood (29 [12.9%] vs. 40 [4.9%], PV<0.001) and attention (30 [13.4%] vs. 68 [8.3%], PV-0.028). None of the symptoms were more prevalent in the younger age group (Table 1S, supplementary material – part B; Figure 2).

Symptoms more prevalent in children without a history of SARS-CoV-2 infection were attention problems with school malfunctioning (225 [10.8%] vs. 98 [8.5%], PV=0.05), stress or increased worries (190 [9.1%] vs. 65 [5.7%], PV<0.001), social problems (164 [7.8%] vs. 32 [2.8%]), weight changes (143 [6.8%] vs. 43 [3.7%], PV<0.001) and sleep disturbances (103 [4.9%], vs. 34 [3%], PV=0.008). All these

symptoms were more prevalent in the older age group. However, in the older age group, all these symptoms were not significantly different between children with or without a history of SARS-CoV-2 infection (Table 1S, supplementary material – part B]).

Symptoms which were not found significantly different between children with or without a history of SARS-CoV-2 infection include decreased mood (69 [6%] vs. 163 [7.8%], PV=0.064), rash (13 [1.1%] vs. 18 [0.9%], PV=0.455, visual disturbances (14 [1.2%] vs. 22 [1.1%], PV=0.727) and hearing problems (0 [0%] vs. 7 [0.3%], PV=0.056).

Multivariate analysis

Factors associated with at least one long-COVID symptom include older age and a history of symptomatic COVID infection. Each one-year increment in age increases the risk in 8% (odds ratio [OR] 1.08, 95% confidence interval (CI) 1.03-1.14, PV=0.001). The history of symptomatic COVID infection increases the risk substantially, OR-4.41, 95% CI 3.27-5.94, PV<0.001) (Table 2S, supplementary material – part B).

Failure (or inability) to return to baseline health status in children with a history of SARS-CoV-2 infection was associated with fatigue (OR-9.71, 95% CI 5.58-16.87, PV<0.001), weight changes (OR- 4.75, 95% CI 1.92-11.76, PV<0.001), decreased social functioning (OR-4.58, 95% CI 1.64-12.77, PV=0.004), dyspnea (OR-3.35, 95% CI 1.16-9.63, PV=0.025), increased stress (OR-2.97, 95% CI 1.37-6.43, PV=0.006), dizziness (OR-2.75, 95% CI 1.17-6.49, PV=0.021), headaches (OR-2.70, 95% CI 1.52-4.80, PV<0.001) and attention disturbances with malfunction in school (OR-2.19, 95% CI 1.12-4.26, PV=0.022) (Table 3S, supplementary material – part B).

Age, gender, time from illness, symptomatic disease, and vaccination status were not associated with not returning to baseline health status in test-positive children.

DISCUSSION

Principal findings

We conducted a nationwide cross-sectional study to assess the prevalence of long-COVID symptoms reported by the parents of children with or without a history of SARS-CoV-2 infection. In addition, we evaluated the factors associated with the presence of any long-COVID symptom and not returning to baseline state of health. Children with a history of SARS-CoV-2 infection had significantly more physical symptoms, including headaches, weakness, fatigue, abdominal pain, cough, myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnea, and increased heart rate. Children without a history of SARS-CoV-2 infection had significantly more functional symptoms, including attention problems with a malfunction in school, stress or increased worries, social problems, weight changes, and sleep disturbances. Almost all symptoms were more prevalent among the older age group than the younger age group.

Factors associated with at least one long-COVID symptom were age and symptomatic SARS-CoV-2 infection. Factors associated with not returning to baseline health status were long-COVID symptoms, including fatigue, weight changes, decreased social functioning, dyspnea, increased stress, dizziness, headache, and attention disturbances with malfunction at school.

Strengths and limitations

The strengths of this study are its nationwide coverage, the relatively large number of participants, the comparison of children with or without a history of SARS-CoV-2 infection, and the broad age range (5 to 18 years old).

This study has several limitations. Firstly, its relatively low response rate (11.9%) and the cross-section design may cause a selection bias. Parents of children with more symptoms might respond more than other parents. Since parents could choose which child they report in the questionnaire, they might have chosen the child with the most symptoms. Secondly, the responses from a proxy (a parent) rather than the child and the potential for differential misclassification bias as parents to children with a history of SARS-CoV-2 infection may report more symptoms than children without a history of SARS-CoV-2 infection. These factors combined might have caused the reported prevalence of long-COVID symptoms to be higher than it is. Thirdly, this study represents only long symptoms related to the Delta and Omicron variants. Different variants might not have the same long-term influence on children. Fourthly, children without a history of SARS-CoV-2 infection might actually have an asymptomatic infection they were unaware of. This, however, gives us a conservative estimation of the difference between the groups. Fifthly, the questionnaire was built by the authors of this study and is not validated. This might also affect the results. In order to overcome some of the abovementioned limitations, especially the possible selection bias, we have compared the parents who did and did not respond to our survey to reduce this possible selection bias.

Interpretation

We report a high rate of at least one long-COVID symptom in both children with or without a history of SARS-CoV-2 infection (43.7% vs. 33.3). This is in line with other studies that found similar rates of long-COVID symptoms, including 35.4% vs.

8.3% in the CLOCK study and 61.9% vs. 57% in the LongCOVIDKidsDK.(9,13) However, other studies reported much lower rates of having at least one long-COVID symptom, including Molteni et al. with only 4.4% after 28 days and 1.8% at 56 days, Radtke et al. with 4% vs. 2%, and Zavala et al. with 6.7% vs. 4.2%.(8,10,12) In Borch et al. study, the prevalence of long-COVID symptoms was 28%. However, the residual difference was only 0.8%, implicating a very low prevalence of long-COVID in children attributable to the infection itself (14). These differences were addressed by Molteni herself and explained by some possible reasons; different study design, different response rates (and thus a better or worse representation of the entire pediatric population), gender imbalance, recall bias, and the higher awareness for this syndrome due to extensive media coverage (15).

The presence of at least five symptoms in our study is 9.9% vs. 4.3%, lower than the rate reported by the CLOCK study (23.7% vs. 3.8%). The age differences in both studies can explain this. The CLOCK focused mainly on adolescents, whereas our study age range was 5-18, with a median age of 10.8 and 9.5 in test-positive and test-negative children, respectively.

The five most prevalent long-COVID symptoms reported by parents of children with vs. without a history of SARS-CoV-2 infection were headaches, weakness, fatigue, abdominal pain, and cough. In Behnood et al.'s meta-analysis, headache, loss of smell, sore throat, and sore eyes were more prevalent in test-positive than test-negative children(7). However, abdominal pain, cough, fatigue, myalgia, insomnia, diarrhea, fever, dizziness, and dyspnea were similarly prevalent in both groups. It is important to note that the LongCOVIDKidsDK was not included in this meta-analysis. In this study, the most prevalent symptoms were dyspnea, cough, sore throat, dizziness, and chest pain (13). Borch et al. reported that fatigue, loss of smell and

taste, muscle weakness, chest pain, dizziness, and respiratory problems were the most reported symptoms (14). The symptoms in children are similar to the symptoms most commonly reported by adults. This includes weakness, general malaise, fatigue, dyspnea, arthralgia, and headache (16–19).

Interestingly, our study found that some symptoms were more prevalent in children without a history of previous SARS-CoV-2 infection, including attention with malfunction in school, stress or increased worries, social problems, weight changes, and sleep disturbances. These are all functional complaints that may reflect life's impact during the pandemic on children. Notably, no significant difference in these symptoms existed in the older age group in adolescents with or without a history of SARS-CoV-2 infection. This is in line with the results of Blankenburg et al., which reported a lack of differences in neurocognitive, general pain, and most mood symptoms with a very high rate of reported symptoms (at least 35%) regardless of serostatus (11). It is also in line with Borch et al., that reported concentration problems to be more prevalent in children without a history of infection (14). This highlights the impact of the pandemic itself, rather than being infected, as a significant source of stress, decreased mood, and poor quality of life for children and adolescents.(20–23)

We found that the presence of any long-COVID symptom was associated with older age and a history of a symptomatic disease but not with gender. Older age and female gender were associated with long-COVID symptoms in children and adolescents in most studies.(7,9–11) In adults, risk factors for long-COVID symptoms include age, female gender, and the history of symptomatic disease. (24–26)

Conclusion

This study suggests that the prevalence of long-COVID symptoms in children with a history of SARS-CoV-2 infection might be higher and more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Contribution Statement

Dr. Adler conceptualized and designed the study, designed the data collection instruments, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Israel designed the data collection instruments, collected data, and reviewed and revised the manuscript.

Dr. Yehoshua, Prof. Azuri, Dr. Hoffman, Dr. Shahar, and Dr. Mizrahi Reuveni conceptualized and designed the study and reviewed and revised the manuscript.

Prof. Grossman conceptualized and designed the study, designed the data collection instruments, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Patient consent for publication: Not required.

Data availability statement: No additional data available.

Ethics statement: The MHS Institutional Review Board (IRB) approved this study (ID 0169-20-MHS).

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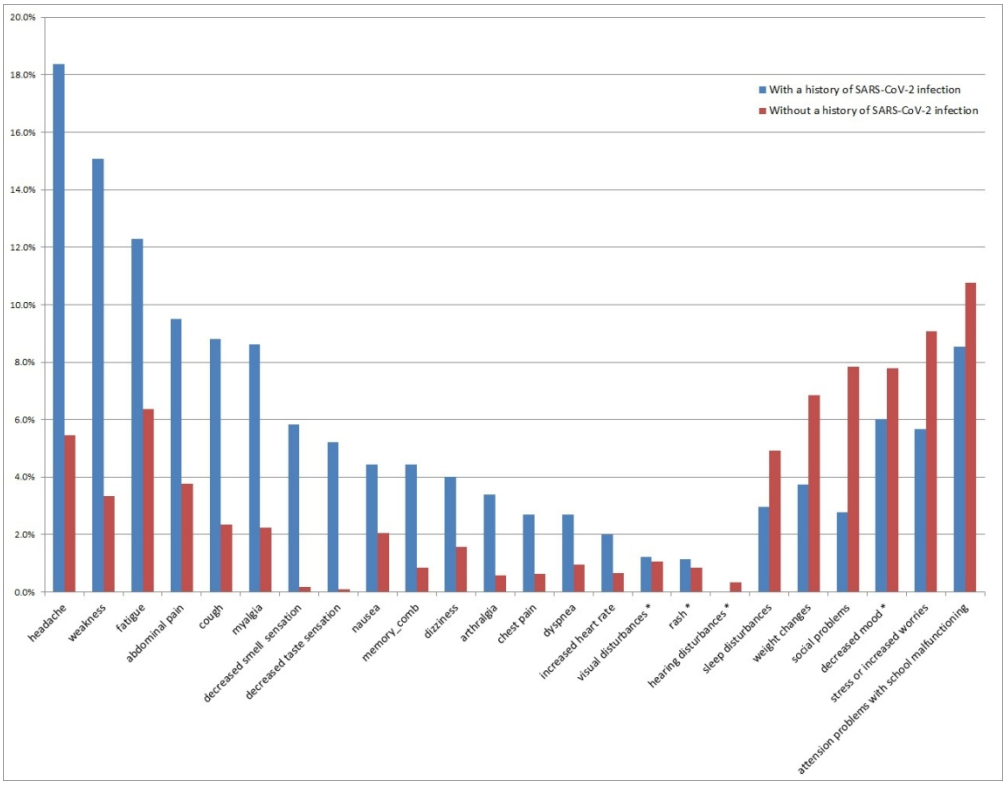
Figure 1. Rates of long-COVID symptoms in children with and without a history of SARS-CoV-2 infection

Long-COVID symptoms with insignificant differences are marked with an asterisk (*).

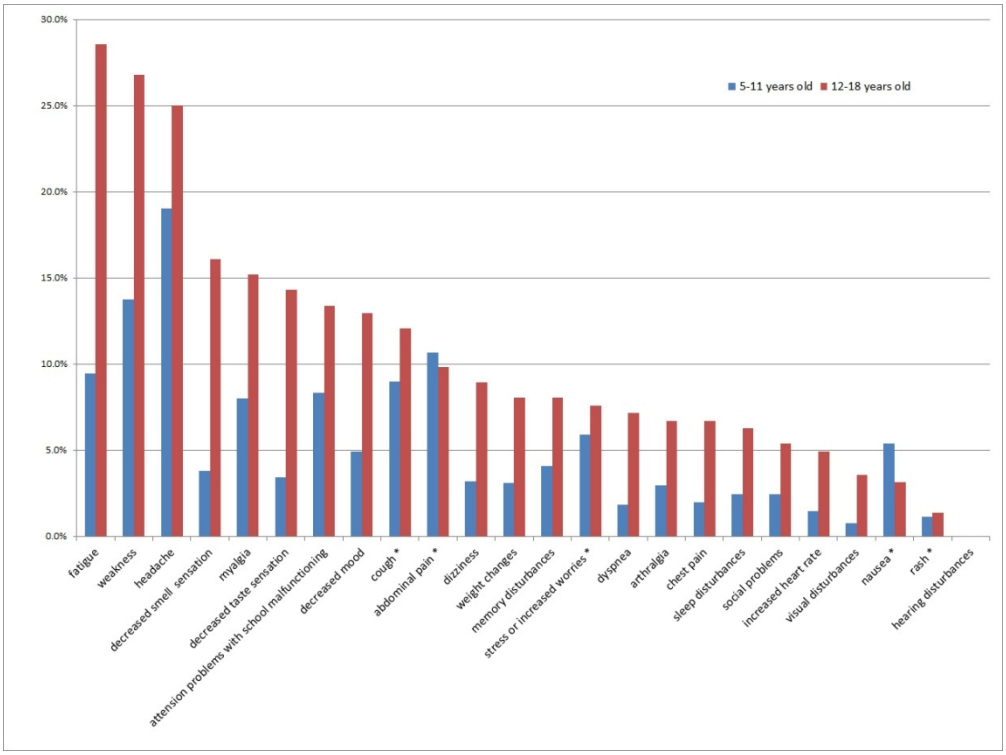
Figure 2. Rates of long-COVID symptoms in children with a history of SARS-CoV-2 infection – a comparison between children aged 5-11 and adolescents aged 12-18

Long-COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).



Long-COVID symptoms with insignificant differences are marked with an asterisk (*).

458x355mm (72 x 72 DPI)



Long-COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).

439x327mm (72 x 72 DPI)

The questionnaires for parents

Do you approve of the participation of your child in this research (Participation in this research means filling out this questionnaire only) Yes/No?

Child's age _____ (Number between 5-18)

Child's Sex: M/F

Refers to a child with Covid 19 infection history:

When did your child have Covid 19 infection? (Month/Year)

During the Covid 19 infection, did your child have any symptoms? Yes/No

During the Covid 19 infection, was your child admitted to the hospital? Yes/No

If the answer is yes, was your child on respiratory support or admitted to PICU? Yes/No

To Covid 19 recovered patients only:

Does your child feel he fully recovered? Yes/No

Do you feel your child fully recovered? Yes/No

Below is a list of symptoms.

Please mark if your child has one or more of the following symptoms, more than he/she had before the Covid 19 infection? Or more than he/she had before the Covid 19 outbreak in Israel?

[all with yes/no options]

- Change in the sense of smell
- Change in the sense of taste
- Headache
- Shortness of breath
- Muscle pains
- Cough
- Rash
- Nausea
- Weakness
- Dizziness
- Joints aches
- Abdominal Pain

- Chest Pain
- Palpitations/Heart racing
- Vision disturbance
- Hearing disturbance
- The child has none of the above

In Addition, please mark if your child has one or more of the following symptoms than he/she had before the Covid 19 infection? Or more than he/she had before the Covid 19 outbreak in Israel?

[all with yes/no options]

- Fatigue
- Sleeping disturbances
- Anxiety or excessive worrying?
- Memory deterioration
- Confusion
- Weight loss or weight gain of more than 3 Kg in the last year
- Attention and/or concentration difficulties in school or kindergarten
- The child has none of the above symptoms

In general, how is your child's health in comparison to the condition before the Covid 19 infection or prior to the Covid 19 outbreak in Israel ?: Same/Better/Worse

Is your child on any chronic medications? Yes/No

If yes, Is the child getting chronic medications for one or more of the following conditions?

- Diabetes mellitus
- Asthma or chronic lung condition
- Chronic inflammatory or autoimmune condition
- Oncologic disorder
- Anxiety or depression
- None of the above

Does your child have or have an oncologic disorder? Yes/No

For 15 years of age or older only: is your child smoking? Yes/No

Was your child born in Israel? Yes/No

Weight: _____ Height: _____

We appreciate your cooperation!

We want to emphasize that this questionnaire is for research purposes only. The answers to the questionnaire are not observed or transferred to medical personnel and are not a replacement for seeking medical advice. In case of symptoms that require medical attention, please see your treating doctor.

We wish you good and full health!

Table 1S. Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection, stratified by age and infection status

	All participants			Participants aged 5-11*			Participants aged 12-18*		
	No history of SARS-CoV2-infection	**With a history of SARS-Cov-2 infection**	**P-value**	**No history of SARS-CoV2-infection**	**With a history of SARS-Cov-2 infection**	**P-value**	**No history of SARS-CoV2-infection**	**With a history of SARS-Cov-2 infection**	**P-value**
	N= 2,092 n (%)	**N= 1,148 n (%)**		**n=1218**	**n=815**		**N=817**	**N=224**	
No reported symptoms	1396 (66.7)	646 (56.3)	<0.001	831 (68.2)	450 (55.2)	<0.001	508 (62.2)	88 (39.3)	<0.001
≥ 1 symptom	696 (33.3)	502 (43.7)		387 (31.8)	365		309 (37.8)	136 (60.7)	

					(44.8)				
≥ 5 symptoms	89 (4.3)	114 (9.9)	<0.001	35 (2.9)	66 (8.1)	<0.001	54 (6.6)	48 (21.4)	<0.001
Current health status compared to before illness/pandemia worse	113 (5.4)	107 (9.3)	<0.001	47 (3.9)	64 (7.9)	<0.001	66 (8.1)	43 (19.2)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection									
Headaches	114 (5.4)	211 (18.4)	<0.001	56 (4.6)	155 (19)	<0.001	58 (7.1)	56 (25%)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001	27 (2.2)	112 (13.7)	<0.001	43 (5.3)	60 (26.8)	<0.001
Fatigue	133 (6.4)	141 (12.3)	<0.001	33 (2.7)	77 (9.4)	<0.001	100 (12.2)	64 (28.6)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001	49 (4)	87 (10.7)	<0.001	30 (3.7)	22 (9.8)	<0.001

Cough	49 (2.3)	101 (8.8)	<0.001	32 (2.6)	73 (9)	<0.001	17 (2.1)	27 (12.1)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001	24 (2)	65 (8)	<0.001	23 (2.8)	34 (15.2)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001	1 (0.1)	31 (3.8)	<0.001	3 (0.4)	36 (16.1)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001	1 (0.1)	28 (3.4)	<0.001	1 (0.1)	32 (14.3)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001	21 (1.7)	44 (5.4)	<0.001	22 (2.7)	7 (3.1)	0.818
Memory disturbances	18 (0.9)	51 (4.4)	<0.001	13 (1.1)	33 (4)	<0.001	5 (0.6)	18 (8)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001	11 (0.9)	26 (3.2)	<0.001	22 (2.7)	20 (8.9)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001	6 (0.5)	24 (2.9)	<0.001	6 (0.7)	15 (6.7)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001	5 (0.4)	16 (2)	<0.001	8 (1)	15 (6.7)	<0.001
Dyspnea	20 (1)	31 (2.7)	<0.001	8 (0.7)	15 (1.8)	0.013	12 (1.5)	16 (7.1)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001	6 (0.5)	12 (1.5)	0.021	8 (1)	11 (4.9)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection									

Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05	133 (10.9)	68 (8.3)	0.057	92 (11.3)	30 (13.4)	0.412
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001	112 (9.2)	48 (5.9)	0.007	78 (9.5)	17 (7.6)	0.433
Social problems	164 (7.8)	32 (2.8)	<0.001	87 (7.1)	20 (2.5)	<0.001	77 (9.4)	12 (5.4)	0.059
Weight changes	143 (6.8)	43 (3.7)	<0.001	71 (5.8)	25 (3.1)	0.004	72 (8.8)	18 (8)	0.789
Sleep disturbance	103 (4.9)	34 (3.0)	0.008	47 (3.9)	20 (2.5)	0.082	56 (6.9)	14 (6.3)	0.768
Symptoms with non-significant results									
Decreased mood	163 (7.8)	69 (6)	0.064	69 (5.7)	40 (4.9)	0.458	94 (11.5)	29 (12.9)	0.560
Rash	18 (0.9)	13 (1.1)	0.455	11 (0.9)	9 (1.1)	0.652	7 (0.9)	3 (1.3)	0.699
Visual disturbance	22 (1.1)	14 (1.2)	0.727	12 (1)	6 (0.7)	0.557	10 (1.2)	8 (3.6)	0.024
Hearing disturbances	7 (0.3)	0 (0)	0.056	4 (0.3)	0 (0)	0.102	3 (0.4)	0 (0)	0.602

*children whose parents did not declare age were excluded from the age stratification

Table 2S. Multivariate analysis of children with a history of SARS-CoV-2 infection who reported at least one symptom of long COVID-19

Variable	Odds Ratio (95% Confidence interval)	P value
Age †	1.08 (1.03, 1.14)	0.001
Sex (female) †	1.12 (0.84, 1.48)	0.442
Time from illness †	0.95 (0.86, 1.05)	0.311
Symptomatic COVID-19 †	4.41 (3.27, 5.94)	<0.001
Vaccination against COVID-19 †	0.87 (0.58, 1.31)	0.512

† Symptomatic disease, age, sex, time from illness, and vaccination status were entered with ENTER method
(*) The presence of diabetes mellitus, asthma, auto-immune disease, a history of malignancy, and native-born were entered with the FORWARD method. None were found significant and entered the final model.

Table 3S. Multivariate analysis of children with a history of SARS-CoV-2 infection who reported their overall health state is worse than before the illness

Variable	Odds Ratio (95% Confidence interval)	P value
Age †	1.06 (0.96, 1.16)	0.257
Sex (female) †	1.06 (0.60, 1.88)	0.833
Time from illness †	0.94 (0.77, 1.16)	0.579
Symptomatic disease †	1.93 (0.93, 4.04)	0.079
Vaccination	1.25 (0.59, 2.65)	0.556
fatigue	9.71 (5.58, 16.87)	<0.001
Weight changes	4.75 (1.92, 11.76)	<0.001
Decreased social function	4.58 (1.64, 12.77)	0.004
Dyspnea ‡	3.35 (1.16, 9.63)	0.025
Increased stress	2.97 (1.37, 6.43)	0.006
Dizziness	2.75 (1.17, 6.49)	0.021
Headache ‡	2.70 (1.52, 4.80)	<0.001
Attention disturbances with impact on functioning in school	2.19 (1.12, 4.26)	0.022

†age, sex, time from illness, symptomatic disease, and vaccination status were entered with ENTER method

‡ Long COVID-19 symptoms (fatigue, decreased smell sensation, decreased taste sensation, headache, dyspnea, myalgia, cough, rash, nausea, weakness, depression, stress, memory disturbances, confusion, dizziness, sleep disturbances, arthralgia, abdominal pain, chest pain, increased heart rate, disturbed vision, hearing disturbances, weight changes, attention disturbances with impact on school and decreased social functioning) were entered with FORWARD method

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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BMJ Open

Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cross-sectional study

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Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cross-sectional study

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ABSTRACT

Objectives To estimate the prevalence of long-COVID symptoms in children with and without a history of SARS-CoV-2 infection and to evaluate factors associated with long-COVID.

Design A nationwide cross-sectional study

Setting Primary care

Participants 3,240 parents of children aged 5-18 with and without SARS-CoV-2 infection completed an online questionnaire (11.9% response rate); 1,148 and 2,092 with/without a history of infection, respectively.

Primary and secondary outcome measures Primary outcome was the prevalence of long-COVID symptoms in children with/without a history of infection. Secondary outcomes were the factors associated with the presence of long-COVID symptoms and with failure to return to baseline health status in children with a history of infection including gender, age, time from illness, symptomatic illness and vaccine status.

Results

Most long-COVID symptoms were more prevalent in children with a history of SARS-CoV-2 infection; headaches (211 [18.4%] vs. 114 [5.4%], p-value [PV]<0.001), weakness (173 [15.1%] vs. 70 [3.3%], PV<0.001), fatigue (141 [12.3%] vs. 133 [6.4%], PV<0.001), and abdominal pain (109 [9.5%] vs. 79 [3.8%], PV<0.001). Most long-COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12-18) compared to the younger age group (5-11). Some symptoms were more prevalent in children without a history of SARS-CoV-2 infection, including attention problems with school malfunctioning (225 [10.8%] vs. 98 [8.5%], PV=0.05), stress (190 [9.1%] vs. 65 [5.7%], PV<0.001),

social problems (164 [7.8%] vs. 32 [2.8%]), and weight changes (143 [6.8%] vs. 43 [3.7%], PV<0.001)

Conclusion

This study suggests that the prevalence of long-COVID symptoms in children with a history of SARS-CoV-2 infection might be higher and more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Strengths and limitations of this study

- A nationwide coverage of participants.
- A relatively large number of participants with a broad age range (5 to 18 years old).
- A comparison of children with or without a history of SARS-CoV-2 infection.
- A relatively low response rate (11.9%) which may cause a selection bias.
- The responses were from a proxy (the parent) rather than the child itself.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in December 2019 and was declared a pandemic by the WHO in March 2020. Evidence emerged slowly but consistently about persistent symptoms following infection and the WHO defined the Post-COVID-19 condition (also known as long-COVID) in October 2021. (1) Reports were first made for adults,(2–4) and later evidence started to emerge regarding the existence of long-COVID in children and adolescents; the first scientific report came from Sweden with a case series by Ludvigsson, who followed five children with a potential long COVID syndrome.(5) First reports were primarily descriptive, with relatively small sample sizes and without a control group.(6)

Behnood et al. performed a meta-analysis of controlled and uncontrolled studies regarding long-COVID in children and adolescents.(7) Among all studies, only five were controlled studies.(8–12) They found a higher prevalence of cognitive difficulties, headache, loss of smell, sore throat, and sore eyes in test-positive children. However, symptoms like abdominal pain, cough, fatigue, myalgia, insomnia, diarrhea, fever, dizziness, or dyspnea were not significantly increased in test-positive children in this study. Controversy later emerged when some of the largest studies about long-COVID in children and adolescents reported different results of prevalence of at least one long-COVID symptom with ranges varying between 1.8% to 61.9% (8–11,13-14).

This study aimed to estimate the prevalence of long-COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection and evaluate factors associated with long-COVID and failure to return to baseline health status.

METHODS

Study design and setting

We designed a nationwide cross-sectional study using the centralized database of Maccabi Healthcare Services (MHS), the second-largest healthcare maintenance organization in Israel, which covers a quarter of Israel's population (2.6 million citizens). We sent an online questionnaire using text messages to parents of children aged 5-18 years old with a positive Polymerase Chain Reaction (PCR) test for SARS-CoV-2 one to six months before data collection. In addition, we sent the questionnaire to a control group of parents of children with no positive PCR results (with a ratio of 1:2). We asked parents to choose one child per family and answer the questionnaire according to his or her health status (The questionnaire is available, supplementary material – part A). The questionnaire did not include questions about other infections. Informed consent was given via the online questionnaire.

Variables

Demographic and medical variables included age, sex, native-born, height, weight, and the presence of any chronic illness (including diabetes mellitus, asthma, inflammatory disease, oncologic disease, anxiety, or depression). COVID-19-related variables included details about the acute illness, including the date of illness, presence of any symptoms (without mentioning which ones), whether the child was admitted to a hospital due to COVID-19, and if so, whether oxygen supply was warranted, and vaccination status against COVID-19. The last section included questions regarding the presence of Long-COVID symptoms (including physical and mental health symptoms, long-COVID symptoms were defined as symptoms lasting more than 4-weeks) and asked parents whether the overall health status of their

children is worse, the same, or better than their baseline health status. We chose to refer to these symptoms as long-COVID symptoms in both groups for reasons of clarity, although long-COVID does not exist in the control group. The questionnaire was created by the authors of this study related to most symptoms reported in the literature.

Statistical analysis

Sample size calculations – to show a difference of relatively rare symptoms, we assumed a prevalence of 0.5% in children without and 3.5% in children with a history of SARS-CoV-2 infection. To show a significant difference with a power of 80% and alpha of 5% with a 2:1 ratio, we needed at least 275 in children with, and 550 in children without a history of SARS-CoV-2 infection. We assumed a prevalence of 5% in children without and 10% in children with a history of SARS-CoV-2 infection for more prevalent symptoms. In the same terms, we needed at least 341 in children with and 682 in children without a history of SARS-CoV-2 infection.

Descriptive statistics were used for all variables, with absolute numbers and percentages for categorical variables and mean and standard deviation for continuous variables. First, we performed univariate analysis to all long-COVID symptoms and compared children with and without a history of SARS-CoV-2 infection using the chi-square test. We then performed the same analysis with age stratification (ages 5-11 and 12-18). Next, we performed two sets of multi-variable tests to examine which factors were associated with having at least one long-COVID symptom and which factors were associated with worse health status than baseline health status. Both analyses were made using a logistic regression analysis with two blocks, the first using all variables (the ENTER approach) for baseline characteristics and forward stepwise selection for more elaborated variables. Last, we performed a univariate

analysis of the differences between parents of children who did and did not answer the questionnaire. We used the Statistical Package for Social Sciences (SPSS) software version 28 for data analysis.

Ethics statement

The MHS Institutional Review Board (IRB) approved this study (ID 0169-20-MHS).

Patient and public involvement

No patients involved.

RESULTS

Study population

In December 2021 and January 2022, we sent the online questionnaire to 27,240 parents of children (8,550 of parents had at least one child with a history of SARS-CoV-2 infection). In Israel, all formal testing (PCR / antigen) are reported and documented in the central database of each HMO. Home antigen tests were available in Israel from January 2021; however, to get a formal certificate of recovery, all people had to have a formal test. Thus, most patients with SARS CoV-2 infection had a formal test.

3,240 parents answered the questionnaire and agreed to participate in the study (11.9% overall response rate, 13.4% in children with and 11.2% in children without a history of infection). Of all respondents, 1,148 children had a history of SARS-CoV-2 infection, and 2,092 children had no history of SARS-CoV-2 infection. The average age of children with and without a history of SARS-CoV-2 infection was 10.8 and 9.5, with 731 (63.7%) and 1,282 (61.3%) females, respectively (Table 1).

Table 1. Characteristics of children with and without a history of SARS-CoV-2 infection

	Children with a history of SARS-CoV-2 infection	**Children without a history of SARS-CoV-2 infection**
	N=1,148	N=2,092
Age, mean ± standard deviation	10.8 ± 0.08	9.5 ± 0.09
Background variables	n (%)	n (%)
Females	731 (63.7)	1,282 (61.3)
Native born	931 (81)	1,635 (78.1)
Any regular medications	88 (7.7)	188 (10.6)
Diabetes mellitus	4 (0.35)	4 (0.2)
asthma	20 (1.7)	21 (1)
Inflammatory / immune disease	6 (0.5)	17 (0.8)
Depression / anxiety	9 (0.8)	18 (0.9)
A history of any oncologic disease	2 (0.2)	4 (0.2)
COVID-related variables	n (%)	n (%)
At least 1 vaccination	172 (15)	1424 (68)
Symptomatic COVID-19	720 (62.7)	
Hospitalization due to COVID-19	4 (0.3)	
Time since COVID-19 infection (months) Mean ± SD Range	 4.39 ± 1.5 Range: 1-12 months	

Parents of children who did or did not fill the questionnaire were different in a few aspects (Table 2); among the respondents, more were females, in higher age groups and were non-Arab and non-Orthodox Jews.

Table 2. Characteristics of parents who did or did not respond to the questionnaire

	Respondents (N=3,778)	Non-respondents (N=23,469)	P value
	n (%)	n (%)	
Females	2,310 (61.1)	12,570 (53.6)	<0.001
Age			
<24	1 (0.03)	9 (0.04)	
25-34	221 (5.8)	1,961 (8.3)	
35-44	1,441 (38.1)	9,216 (39.3)	<0.001
45-54	1,749 (46.3)	10,080 (42.9)	
>55	366 (9.7)	2,203 (9.4)	
Sector			
Orthodox-Jewish	115 (3)	841 (3.6)	
Arab	109 (2.9)	1,912 (8.1)	<0.001
All other	3,554 (94.1)	20,716 (88.3)	

Of all children with a history of SARS-CoV-2 infection, 720 (62.7%) had symptomatic COVID-19, four were hospitalized due to COVID-19 (0.3%), and 1 needed oxygen supply. The mean duration between infection and answering the questionnaire was 4.4 months. Overall, 696 (33.3%) children without and 502 (43.7%) children with a history of SARS-CoV-2 infection reported at least one symptom (PV<0.001) and 89 (4.3%) children without and 114 (9.9%) children with a history of SARS-CoV-2 infection reported at least five symptoms (PV<0.001). In addition, 113 (5.4%) children without and 107 (9.3%) children with a history of

SARS-CoV-2 infection reported an inability to return to their baseline health status (PV<0.001) (Table 3).

Table 3. Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection

	No history of SARS-CoV2-infection	**With a history of SARS-Cov-2 infection**	**P-value**
	N= 2,092 n (%)	**N= 1,148 n (%)**	
No reported symptoms	1396 (66.7)	646 (56.3)	
≥ 1 symptom	696 (33.3)	502 (43.7)	<0.001
≥ 5 symptoms	89 (4.3)	114 (9.9)	<0.001
Current health status compared to before illness/pandemia - worse	113 (5.4)	107 (9.3)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection			
Headaches	114 (5.4)	211 (18.4)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001
Fatigue	133 (6.4)	141 (12.3)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001
Cough	49 (2.3)	101 (8.8)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001
Memory disturbances	18 (0.9)	51 (4.4)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001
Dyspnea	20 (1)	31 (2.7)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection			

Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001
Social problems	164 (7.8)	32 (2.8)	<0.001
Weight changes	143 (6.8)	43 (3.7)	<0.001
Sleep disturbance	103 (4.9)	34 (3.0)	0.008
Symptoms with non-significant results			
Decreased mood	163 (7.8)	69 (6)	0.064
Rash	18 (0.9)	13 (1.1)	0.455
Visual disturbance	22 (1.1)	14 (1.2)	0.727
Hearing disturbances	7 (0.3)	0 (0)	0.056

Long-COVID symptoms

The five most prevalent long-COVID symptoms reported by parents of children with compared to children without a history of SARS-CoV-2 infection were headaches (211 [18.4%] vs. 114 [5.4%], PV<0.001), weakness (173 [15.1%] vs. 70 [3.3%], PV<0.001), fatigue (141 [12.3%] vs. 133 [6.4%], PV<0.001), abdominal pain (109 [9.5%] vs. 79 [3.8%], PV<0.001) and cough (101 [8.8%] vs. 49 [2.3%], PV<0.001) (Figure 1). Other more prevalent symptoms in children with a history of SARS-CoV-2 infection were myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnea, and increased heart rate (Table 3).

Most long-COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12-18) compared to the younger age group (5-11), including headaches (56 [25%] vs. 155 [19%], PV-0.05), weakness (60 [26.8%] vs. 112 [13.7%], PV<0.001), fatigue (64 [28.6%] vs. 77 [9.4%], PV<0.001), taste (32 [14.3%] vs. 28 [3.4%], PV<0.001), smell (36 [16.1%] vs. 31 [3.8%], PV<0.001), myalgia (34 [15.2%] vs. 65 [8%], PV-0.002), decreased mood (29

[12.9%] vs. 40 [4.9%], PV<0.001) and attention (30 [13.4%] vs. 68 [8.3%], PV-0.028). None of the symptoms were more prevalent in the younger age group (Table 1S, supplementary material – part B; Figure 2).

Symptoms more prevalent in children without a history of SARS-CoV-2 infection were attention problems with school malfunctioning (225 [10.8%] vs. 98 [8.5%], PV=0.05), stress or increased worries (190 [9.1%] vs. 65 [5.7%], PV<0.001), social problems (164 [7.8%] vs. 32 [2.8%]), weight changes (143 [6.8%] vs. 43 [3.7%], PV<0.001) and sleep disturbances (103 [4.9%], vs. 34 [3%], PV=0.008). All these symptoms were more prevalent in the older age group. However, in the older age group, all these symptoms were not significantly different between children with or without a history of SARS-CoV-2 infection (Table 1S, supplementary material – part B]).

Symptoms which were not found significantly different between children with or without a history of SARS-CoV-2 infection include decreased mood (69 [6%] vs. 163 [7.8%], PV=0.064), rash (13 [1.1%] vs. 18 [0.9%], PV=0.455, visual disturbances (14 [1.2%] vs. 22 [1.1%], PV=0.727) and hearing problems (0 [0%] vs. 7 [0.3%], PV=0.056).

Multivariate analysis

Factors associated with at least one long-COVID symptom include older age and a history of symptomatic COVID infection. Each one-year increment in age increases the risk in 8% (odds ratio [OR] 1.08, 95% confidence interval (CI) 1.03-1.14, PV=0.001). The history of symptomatic COVID infection increases the risk substantially, OR-4.41, 95% CI 3.27-5.94, PV<0.001) (Table 2S, supplementary material – part B).

Failure (or inability) to return to baseline health status in children with a history of SARS-CoV-2 infection was associated with fatigue (OR-9.71, 95% CI 5.58-16.87, PV<0.001), weight changes (OR- 4.75, 95% CI 1.92-11.76, PV<0.001), decreased social functioning (OR-4.58, 95% CI 1.64-12.77, PV=0.004), dyspnea (OR-3.35, 95% CI 1.16-9.63, PV=0.025), increased stress (OR-2.97, 95% CI 1.37-6.43, PV=0.006), dizziness (OR-2.75, 95% CI 1.17-6.49, PV=0.021), headaches (OR-2.70, 95% CI 1.52-4.80, PV<0.001) and attention disturbances with malfunction in school (OR-2.19, 95% CI 1.12-4.26, PV=0.022) (Table 3S, supplementary material – part B). Age, gender, time from illness, symptomatic disease, and vaccination status were not associated with not returning to baseline health status in test-positive children.

DISCUSSION

Principal findings

We conducted a nationwide cross-sectional study to assess the prevalence of long-COVID symptoms reported by the parents of children with or without a history of SARS-CoV-2 infection. In addition, we evaluated the factors associated with the presence of any long-COVID symptom and not returning to baseline state of health. Children with a history of SARS-CoV-2 infection had significantly more physical symptoms, including headaches, weakness, fatigue, abdominal pain, cough, myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnea, and increased heart rate. Children without a history of SARS-CoV-2 infection had significantly more functional symptoms, including attention problems with a malfunction in school, stress or increased worries, social problems, weight changes, and sleep disturbances. Almost all symptoms were more prevalent among the older age group than the younger age group.

Factors associated with at least one long-COVID symptom were age and symptomatic SARS-CoV-2 infection. Factors associated with not returning to baseline health status were long-COVID symptoms, including fatigue, weight changes, decreased social functioning, dyspnea, increased stress, dizziness, headache, and attention disturbances with malfunction at school.

Strengths and limitations

The strengths of this study are its nationwide coverage, the relatively large number of participants, the comparison of children with or without a history of SARS-CoV-2 infection, and the broad age range (5 to 18 years old).

This study has several limitations. Firstly, its relatively low response rate (11.9%) and the cross-section design may cause a selection bias. Parents of children with more symptoms might respond more than other parents. Since parents could choose which child they report in the questionnaire, they might have chosen the child with the most symptoms. Secondly, the responses from a proxy (a parent) rather than the child and the potential for differential misclassification bias as parents to children with a history of SARS-CoV-2 infection may report more symptoms than children without a history of SARS-CoV-2 infection. These factors combined might have caused the reported prevalence of long-COVID symptoms to be higher than it is. Thirdly, this study represents only long symptoms related to the Delta and Omicron variants. Different variants might not have the same long-term influence on children. Fourthly, children without a history of SARS-CoV-2 infection might actually have an asymptomatic infection they were unaware of. This, however, gives us a conservative estimation of the difference between the groups. Fifthly, the questionnaire was built by the authors of this study and is not validated. This might also affect the results. In order to overcome some of the abovementioned limitations, especially the possible selection

bias, we have compared the parents who did and did not respond to our survey to reduce this possible selection bias.

Interpretation

We report a high rate of at least one long-COVID symptom in both children with or without a history of SARS-CoV-2 infection (43.7% vs. 33.3). This is in line with other studies that found similar rates of long-COVID symptoms, including 35.4% vs. 8.3% in the CLOCK study and 61.9% vs. 57% in the LongCOVIDKidsDK.(9,13) However, other studies reported much lower rates of having at least one long-COVID symptom, including Molteni et al. with only 4.4% after 28 days and 1.8% at 56 days, Radtke et al. with 4% vs. 2%, and Zavala et al. with 6.7% vs. 4.2%.(8,10,12) In Borch et al. study, the prevalence of long-COVID symptoms was 28%. However, the residual difference was only 0.8%, implicating a very low prevalence of long-COVID in children attributable to the infection itself (14). These differences were addressed by Molteni herself and explained by some possible reasons; different study design, different response rates (and thus a better or worse representation of the entire pediatric population), gender imbalance, recall bias, and the higher awareness for this syndrome due to extensive media coverage (15).

The presence of at least five symptoms in our study is 9.9% vs. 4.3%, lower than the rate reported by the CLOCK study (23.7% vs. 3.8%). The age differences in both studies can explain this. The CLOCK focused mainly on adolescents, whereas our study age range was 5-18, with a median age of 10.8 and 9.5 in test-positive and test-negative children, respectively.

The five most prevalent long-COVID symptoms reported by parents of children with vs. without a history of SARS-CoV-2 infection were headaches, weakness, fatigue, abdominal pain, and cough. In Behnood et al.'s meta-analysis, headache, loss of

smell, sore throat, and sore eyes were more prevalent in test-positive than test-negative children(7). However, abdominal pain, cough, fatigue, myalgia, insomnia, diarrhea, fever, dizziness, and dyspnea were similarly prevalent in both groups. It is important to note that the LongCOVIDKidsDK was not included in this meta-analysis. In this study, the most prevalent symptoms were dyspnea, cough, sore throat, dizziness, and chest pain (13). Borch et al. reported that fatigue, loss of smell and taste, muscle weakness, chest pain, dizziness, and respiratory problems were the most reported symptoms (14). The symptoms in children are similar to the symptoms most commonly reported by adults. This includes weakness, general malaise, fatigue, dyspnea, arthralgia, and headache (16–19).

Interestingly, our study found that some symptoms were more prevalent in children without a history of previous SARS-CoV-2 infection, including attention with malfunction in school, stress or increased worries, social problems, weight changes, and sleep disturbances. These are all functional complaints that may reflect life's impact during the pandemic on children. Notably, no significant difference in these symptoms existed in the older age group in adolescents with or without a history of SARS-CoV-2 infection. This is in line with the results of Blankenburg et al., which reported a lack of differences in neurocognitive, general pain, and most mood symptoms with a very high rate of reported symptoms (at least 35%) regardless of serostatus (11). It is also in line with Borch et al., that reported concentration problems to be more prevalent in children without a history of infection (14). This highlights the impact of the pandemic itself, rather than being infected, as a significant source of stress, decreased mood, and poor quality of life for children and adolescents.(20–23)

We found that the presence of any long-COVID symptom was associated with older age and a history of a symptomatic disease but not with gender. Older age and female gender were associated with long-COVID symptoms in children and adolescents in most studies.(7,9–11) In adults, risk factors for long-COVID symptoms include age, female gender, and the history of symptomatic disease. (24–26)

Conclusion

This study suggests that the prevalence of long-COVID symptoms in children with a history of SARS-CoV-2 infection might be higher and more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Contribution Statement

Dr. Adler conceptualized and designed the study, designed the data collection instruments, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Israel designed the data collection instruments, collected data, and reviewed and revised the manuscript.

Dr. Yehoshua, Prof. Azuri, Dr. Hoffman, Dr. Shahar, and Dr. Mizrahi Reuveni conceptualized and designed the study and reviewed and revised the manuscript.

Prof. Grossman conceptualized and designed the study, designed the data collection instruments, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Patient consent for publication: Not required.

Data availability statement: No additional data available.

Ethics statement: The MHS Institutional Review Board (IRB) approved this study (ID 0169-20-MHS).

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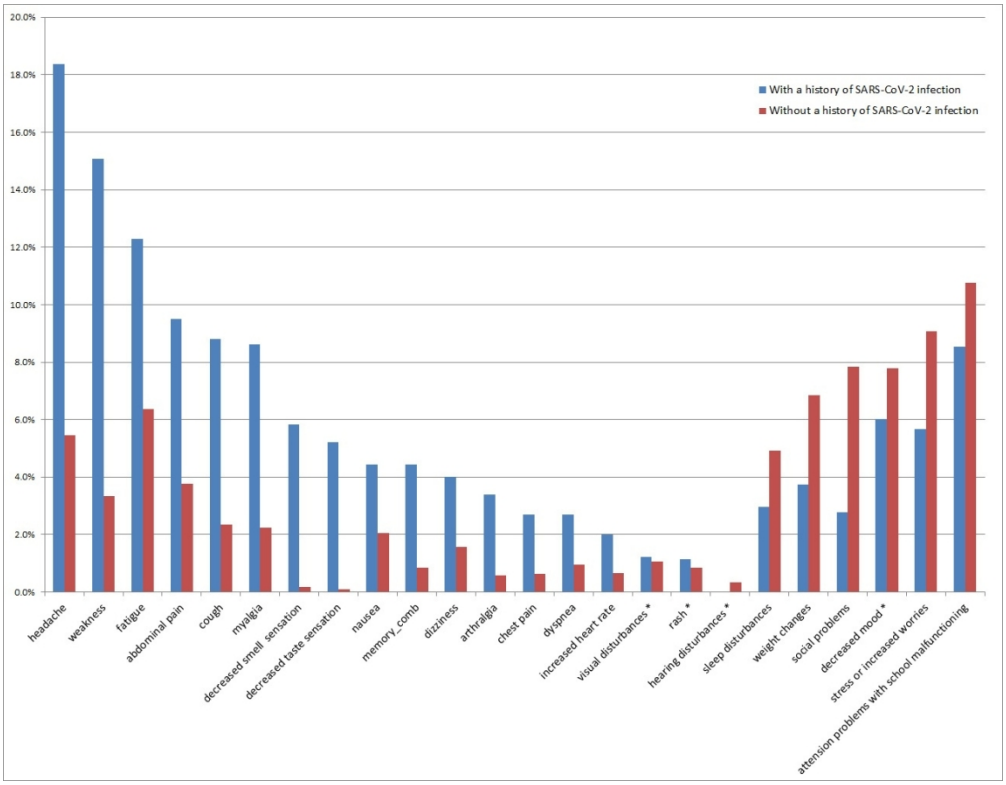
Figure 1. Rates of long-COVID symptoms in children with and without a history of SARS-CoV-2 infection

Long-COVID symptoms with insignificant differences are marked with an asterisk (*).

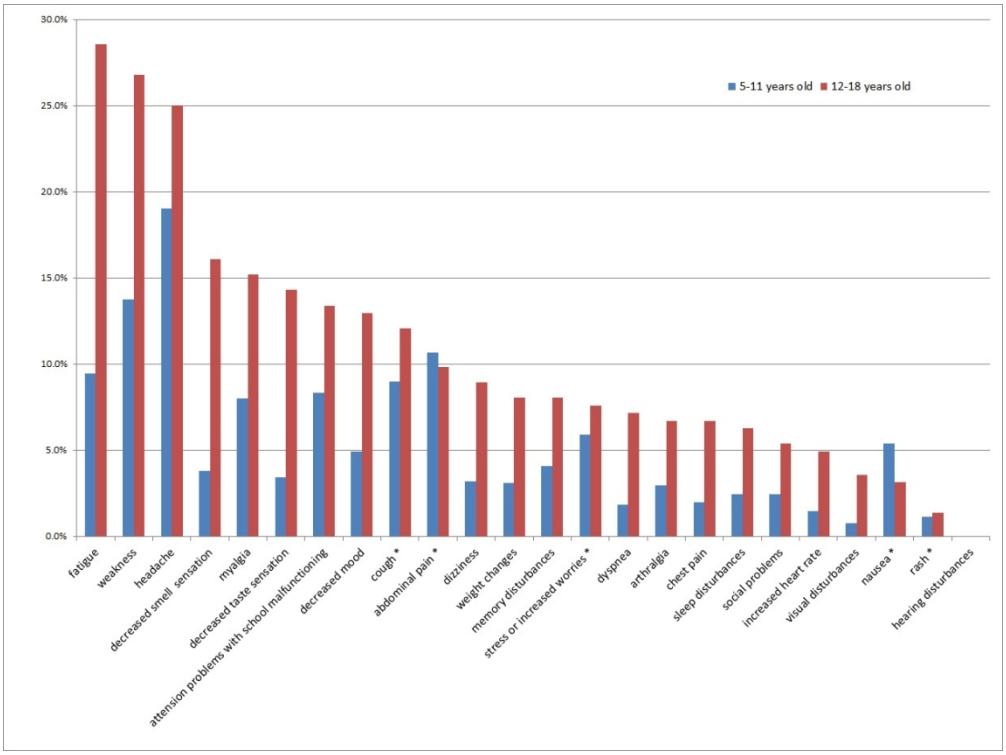
Figure 2. Rates of long-COVID symptoms in children with a history of SARS-CoV-2 infection – a comparison between children aged 5-11 and adolescents aged 12-18

Long-COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).



Long-COVID symptoms with insignificant differences are marked with an asterisk (*).

458x355mm (72 x 72 DPI)



Long-COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).

439x327mm (72 x 72 DPI)

The questionnaires for parents

Do you approve of the participation of your child in this research (Participation in this research means filling out this questionnaire only) Yes/No?

Child's age _____ (Number between 5-18)

Child's Sex: M/F

Refers to a child with Covid 19 infection history:

When did your child have Covid 19 infection? (Month/Year)

During the Covid 19 infection, did your child have any symptoms? Yes/No

During the Covid 19 infection, was your child admitted to the hospital? Yes/No

If the answer is yes, was your child on respiratory support or admitted to PICU? Yes/No

To Covid 19 recovered patients only:

Does your child feel he fully recovered? Yes/No

Do you feel your child fully recovered? Yes/No

Below is a list of symptoms.

Please mark if your child has one or more of the following symptoms, more than he/she had before the Covid 19 infection? Or more than he/she had before the Covid 19 outbreak in Israel?

[all with yes/no options]

- Change in the sense of smell
- Change in the sense of taste
- Headache
- Shortness of breath
- Muscle pains
- Cough
- Rash
- Nausea
- Weakness
- Dizziness
- Joints aches
- Abdominal Pain

- Chest Pain
- Palpitations/Heart racing
- Vision disturbance
- Hearing disturbance
- The child has none of the above

In Addition, please mark if your child has one or more of the following symptoms than he/she had before the Covid 19 infection? Or more than he/she had before the Covid 19 outbreak in Israel?

[all with yes/no options]

- Fatigue
- Sleeping disturbances
- Anxiety or excessive worrying?
- Memory deterioration
- Confusion
- Weight loss or weight gain of more than 3 Kg in the last year
- Attention and/or concentration difficulties in school or kindergarten
- The child has none of the above symptoms

In general, how is your child's health in comparison to the condition before the Covid 19 infection or prior to the Covid 19 outbreak in Israel ?: Same/Better/Worse

Is your child on any chronic medications? Yes/No

If yes, Is the child getting chronic medications for one or more of the following conditions?

- Diabetes mellitus
- Asthma or chronic lung condition
- Chronic inflammatory or autoimmune condition
- Oncologic disorder
- Anxiety or depression
- None of the above

Does your child have or have an oncologic disorder? Yes/No

For 15 years of age or older only: is your child smoking? Yes/No

Was your child born in Israel? Yes/No

Weight: _____ Height: _____

We appreciate your cooperation!

We want to emphasize that this questionnaire is for research purposes only. The answers to the questionnaire are not observed or transferred to medical personnel and are not a replacement for seeking medical advice. In case of symptoms that require medical attention, please see your treating doctor.

We wish you good and full health!

Table 1S. Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection, stratified by age and infection status

	All participants			Participants aged 5-11*			Participants aged 12-18*		
	No history of SARS-CoV2-infection	**With a history of SARS-Cov-2 infection**	**P-value**	**No history of SARS-CoV2-infection**	**With a history of SARS-Cov-2 infection**	**P-value**	**No history of SARS-CoV2-infection**	**With a history of SARS-Cov-2 infection**	**P-value**
	N= 2,092 n (%)	**N= 1,148 n (%)**		**n=1218**	**n=815**		**N=817**	**N=224**	
No reported symptoms	1396 (66.7)	646 (56.3)	<0.001	831 (68.2)	450 (55.2)	<0.001	508 (62.2)	88 (39.3)	<0.001
≥ 1 symptom	696 (33.3)	502 (43.7)		387 (31.8)	365		309 (37.8)	136 (60.7)	

					(44.8)				
≥ 5 symptoms	89 (4.3)	114 (9.9)	<0.001	35 (2.9)	66 (8.1)	<0.001	54 (6.6)	48 (21.4)	<0.001
Current health status compared to before illness/pandemia worse	113 (5.4)	107 (9.3)	<0.001	47 (3.9)	64 (7.9)	<0.001	66 (8.1)	43 (19.2)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection									
Headaches	114 (5.4)	211 (18.4)	<0.001	56 (4.6)	155 (19)	<0.001	58 (7.1)	56 (25%)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001	27 (2.2)	112 (13.7)	<0.001	43 (5.3)	60 (26.8)	<0.001
Fatigue	133 (6.4)	141 (12.3)	<0.001	33 (2.7)	77 (9.4)	<0.001	100 (12.2)	64 (28.6)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001	49 (4)	87 (10.7)	<0.001	30 (3.7)	22 (9.8)	<0.001

Cough	49 (2.3)	101 (8.8)	<0.001	32 (2.6)	73 (9)	<0.001	17 (2.1)	27 (12.1)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001	24 (2)	65 (8)	<0.001	23 (2.8)	34 (15.2)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001	1 (0.1)	31 (3.8)	<0.001	3 (0.4)	36 (16.1)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001	1 (0.1)	28 (3.4)	<0.001	1 (0.1)	32 (14.3)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001	21 (1.7)	44 (5.4)	<0.001	22 (2.7)	7 (3.1)	0.818
Memory disturbances	18 (0.9)	51 (4.4)	<0.001	13 (1.1)	33 (4)	<0.001	5 (0.6)	18 (8)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001	11 (0.9)	26 (3.2)	<0.001	22 (2.7)	20 (8.9)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001	6 (0.5)	24 (2.9)	<0.001	6 (0.7)	15 (6.7)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001	5 (0.4)	16 (2)	<0.001	8 (1)	15 (6.7)	<0.001
Dyspnea	20 (1)	31 (2.7)	<0.001	8 (0.7)	15 (1.8)	0.013	12 (1.5)	16 (7.1)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001	6 (0.5)	12 (1.5)	0.021	8 (1)	11 (4.9)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection									

Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05	133 (10.9)	68 (8.3)	0.057	92 (11.3)	30 (13.4)	0.412
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001	112 (9.2)	48 (5.9)	0.007	78 (9.5)	17 (7.6)	0.433
Social problems	164 (7.8)	32 (2.8)	<0.001	87 (7.1)	20 (2.5)	<0.001	77 (9.4)	12 (5.4)	0.059
Weight changes	143 (6.8)	43 (3.7)	<0.001	71 (5.8)	25 (3.1)	0.004	72 (8.8)	18 (8)	0.789
Sleep disturbance	103 (4.9)	34 (3.0)	0.008	47 (3.9)	20 (2.5)	0.082	56 (6.9)	14 (6.3)	0.768
Symptoms with non-significant results									
Decreased mood	163 (7.8)	69 (6)	0.064	69 (5.7)	40 (4.9)	0.458	94 (11.5)	29 (12.9)	0.560
Rash	18 (0.9)	13 (1.1)	0.455	11 (0.9)	9 (1.1)	0.652	7 (0.9)	3 (1.3)	0.699
Visual disturbance	22 (1.1)	14 (1.2)	0.727	12 (1)	6 (0.7)	0.557	10 (1.2)	8 (3.6)	0.024
Hearing disturbances	7 (0.3)	0 (0)	0.056	4 (0.3)	0 (0)	0.102	3 (0.4)	0 (0)	0.602

*children whose parents did not declare age were excluded from the age stratification

Table 2S. Multivariate analysis of children with a history of SARS-CoV-2 infection who reported at least one symptom of long COVID-19

Variable	Odds Ratio (95% Confidence interval)	P value
Age †	1.08 (1.03, 1.14)	0.001
Sex (female) †	1.12 (0.84, 1.48)	0.442
Time from illness †	0.95 (0.86, 1.05)	0.311
Symptomatic COVID-19 †	4.41 (3.27, 5.94)	<0.001
Vaccination against COVID-19 †	0.87 (0.58, 1.31)	0.512

† Symptomatic disease, age, sex, time from illness, and vaccination status were entered with ENTER method
(*) The presence of diabetes mellitus, asthma, auto-immune disease, a history of malignancy, and native-born were entered with the FORWARD method. None were found significant and entered the final model.

Table 3S. Multivariate analysis of children with a history of SARS-CoV-2 infection who reported their overall health state is worse than before the illness

Variable	Odds Ratio (95% Confidence interval)	P value
Age †	1.06 (0.96, 1.16)	0.257
Sex (female) †	1.06 (0.60, 1.88)	0.833
Time from illness †	0.94 (0.77, 1.16)	0.579
Symptomatic disease †	1.93 (0.93, 4.04)	0.079
Vaccination	1.25 (0.59, 2.65)	0.556
fatigue	9.71 (5.58, 16.87)	<0.001
Weight changes	4.75 (1.92, 11.76)	<0.001
Decreased social function	4.58 (1.64, 12.77)	0.004
Dyspnea ‡	3.35 (1.16, 9.63)	0.025
Increased stress	2.97 (1.37, 6.43)	0.006
Dizziness	2.75 (1.17, 6.49)	0.021
Headache ‡	2.70 (1.52, 4.80)	<0.001
Attention disturbances with impact on functioning in school	2.19 (1.12, 4.26)	0.022

†age, sex, time from illness, symptomatic disease, and vaccination status were entered with ENTER method

‡ Long COVID-19 symptoms (fatigue, decreased smell sensation, decreased taste sensation, headache, dyspnea, myalgia, cough, rash, nausea, weakness, depression, stress, memory disturbances, confusion, dizziness, sleep disturbances, arthralgia, abdominal pain, chest pain, increased heart rate, disturbed vision, hearing disturbances, weight changes, attention disturbances with impact on school and decreased social functioning) were entered with FORWARD method

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.